

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/23277

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 760 025 A (INST NAT SANTE RECH MED) 28 August 1998 (1998-08-28) the whole document ---	1-55
A	WO 96 28571 A (RECH INVESTISSEMENT SOC FR DE ;PROVOT CHRISTIAN (FR); SALLES BERNARD) 19 September 1996 (1996-09-19) the whole document ---	1-55
A	EP 0 628 817 A (TNO) 14 December 1994 (1994-12-14) the whole document ---	1-55 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

24 February 2000

09/03/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
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Authorized officer

Hagenmaier, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/23277

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>MICHELOTTI ET AL.: "MULTIPLE SINGLE-STRANDED CIS-ELEMENTS ARE ASSOCIATED WITH ACTIVATED CHROMATIN OF THE HUMAN C-MYC GENE IN VIVO" <i>MOL.CELL.BIOL.</i>, vol. 16, no. 6, 1996, pages 2656-2669, XP002131441 the whole document</p> <p>---</p>	1-55
A	<p>EVANS ET AL.: "S1-HYPERSENSITIVE SITES IN EUKARYOTIC PROMOTER REGIONS" <i>NUCLEIC ACIDS RESEARCH</i>, vol. 12, no. 21, 1984, pages 8043-8058, XP002131122 the whole document</p> <p>---</p>	1-55
A	<p>STEWART ET AL.: "RAPID INDUCTION OF c-fos TRANSCRIPTION REVEALS QUANTITATIVE LINKAGE OF RNA POLYMERASE II AND DNA TOPOISOMERASE I ENZYME ACTIVITIES" <i>CELL</i>, vol. 60, 1990, pages 141-149, XP002131034 the whole document</p> <p>---</p>	1-55
A	<p>WANG AND ROEDER: "DNA TOPOISOMERASE I AND PC4 CAN INTERACT WITH HUMAN TFIIIC TO PROMOTE BOTH ACCURATE TERMINATION AND TRANSCRIPTION REINITIATION BY RNA POLYMERASE III" <i>MOL.CELL</i>, vol. 1, April 1998 (1998-04), pages 749-757, XP002131035 the whole document</p> <p>---</p>	1-55
A	<p>FRIEDBERG E C: "RELATIONSHIPS BETWEEN DNA REPAIR AND TRANSCRIPTION" <i>ANNUAL REVIEW OF BIOCHEMISTRY</i>, US, PALTO ALTO, CA, vol. 65, 1 January 1996 (1996-01-01), pages 15-42, XP002047711 the whole document</p> <p>---</p>	1-55
A	<p>EP 0 441 483 A (BAYLOR COLLEGE MEDICINE) 14 August 1991 (1991-08-14) the whole document</p> <p>---</p>	1-55

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte .onal Application No

PCT/US 99/23277

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
FR 2760025	A	28-08-1998	W0	9837233 A		27-08-1998
WO 9628571	A	19-09-1996	FR	2731711 A	20-09-1996	
			AU	5008996 A	02-10-1996	
			CA	2215493 A	19-09-1996	
			EP	0815260 A	07-01-1998	
			JP	11510362 T	14-09-1999	
EP 0628817	A	14-12-1994		NONE		
EP 0441483	A	14-08-1991	AU	4493393 A	18-11-1993	
			AU	637446 B	27-05-1993	
			AU	6935291 A	18-07-1991	
			CA	2034220 A	17-07-1991	
			EP	0752477 A	08-01-1997	
			JP	6022766 A	01-02-1994	

Re Item III

Claim 1 does not appear to satisfy Art 5 PCT, because the presence of a nick in a DNA molecule is not in all cases caused by a transcription factor. Mutagenic agents, oxidative stress, radiation (see e.g. D3 p 21 37-41) or DNA-topoisomerase II activity for example introduce nicks in a DNA molecule. Hence, it is not possible to conclude that there is transcription activity if a nick is detected in a DNA molecule. Consequently, the method as defined in claim 1 is insufficient to enable the skilled person to carry out the invention (Guidelines II 4.10). The same argument applies to the dependent **claims 2-9**.

Similarly, the methods of independent **claims 15** and **46** conclude from the detection of nicks in a DNA template that an active transcription factor is present in the reaction mixture. As nicks can be caused by various agents (see above), these claims and the corresponding dependent **claims 16-20, 47-54** do not comply with Art 5 PCT, either. As **claim 55** relies on the method of claim 46, it does not comply with Art 5 PCT either. Consequently, no meaningful opinion can be formed on novelty, inventive step and industrial applicability of the above claims (Art 34 (4)(a)(ii) PCT).

Re Item V

The following documents are referred to in this communication:

- D1: WO 90/05745
- D2: Cell (1988) 53 907-920
- D3: EP-A-0 628 817
- D4: Nucl. Acids Res. (1994) 22(7) 1305-1312
- D5: Fr-A-2 760 025

D1, D2 and D4 are cited by the examiner (Guidelines VI 7.24). A copy of each of D1, D2 and D4 is appended to this written opinion.

1 Novelty (Art 33(2)PCT):

1.1 **Claim 21** is not novel in view of D1 (D1: claims 10 and 11).

A DNA sequence to be transcribed comprising a consensus binding site for a

PATENT COOPERATION TREATY

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NOV 08 1999

LIMBACH & LIMBACH L.L.P.

PCT

**NOTIFICATION OF RECEIPT OF
RECORD COPY**
(PCT Rule 24.2(a))

From the INTERNATIONAL BUREAU

To:

WARD, Michael, R.
Limbach & Limbach L.L.P.
2001 Ferry Building
San Francisco, CA 94111-4262
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year)
01 November 1999 (01.11.99)

IMPORTANT NOTIFICATION

Applicant's or agent's file reference
XGEN-110 PCT

International application No.
PCT/US99/23277

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

XGENE CORPORATION (for all designated States except US)
HOEFFLER, Warren (for US)

International filing date : 06 October 1999 (06.10.99)
Priority date(s) claimed : 09 October 1998 (09.10.98)
Date of receipt of the record copy by the International Bureau : 26 October 1999 (26.10.99)

List of designated Offices :

AP :GH,GM,KE,LS,MW,SD,SL,SZ,TZ,UG,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
National :AE,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EE,ES,FI,GB,
GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,
MW,MX,NO,NZ,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,US,UZ,VN,YU,ZA,ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

time limits for entry into the national phase
 confirmation of precautionary designations
 requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No. (41-22) 740.14.35

Authorized officer:

Eugénia Santos
Telephone No. (41-22) 338.83.38

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. **It is the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

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JAN 3 2000

Limbach & Limbach

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

WARD, Michael, R.
Limbach & Limbach L.L.P.
2001 Ferry Building
San Francisco, CA 94111-4262
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year)
11 November 1999 (11.11.99)

Applicant's or agent's file reference
XGEN-110 PCT

IMPORTANT NOTIFICATION

International application No.
PCT/US99/23277

International filing date (day/month/year)
06 October 1999 (06.10.99)

International publication date (day/month/year)
Not yet published

Priority date (day/month/year)
09 October 1998 (09.10.98) ✓
EF

Applicant

XGENE CORPORATION et al

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date

Priority application No.

Country or regional Office
or PCT receiving Office

Date of receipt
of priority document

09 Octo 1998 (09.10.98)

60/103,803

US

09 Nove 1999 (09.11.99)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Carlos Naranjo

Telephone No. (41-22) 338.83.38

CN

PATENT COOPERATION TREATY

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

WARD, Michael, R.
Limbach & Limbach L.L.P.
2001 Ferry Building
San Francisco, CA 94111-4262
ETATS-UNIS D'AMERIQUE

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MAY 05 2000

Limbach & Limbach

Date of mailing (day/month/year)
20 April 2000 (20.04.00)

Applicant's or agent's file reference
XGEN-110 PCT

IMPORTANT NOTICE

International application No.
PCT/US99/23277

International filing date (day/month/year)
06 October 1999 (06.10.99)

Priority date (day/month/year)
09 October 1998 (09.10.98)

Applicant

XGENE CORPORATION et al

30 mo due 4/9/01 on cd

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AU,CN,JP,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,
GH,GM,HR,HU,ID,IL,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,
PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 20 April 2000 (20.04.00) under No. WO 00/22167

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

J. Zahra

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

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MAR 20 2000

PCT

LIMBACH & LIMBACH L.L.P.

From the INTERNATIONAL SEARCHING AUTHORITY

To:
 LIMBACH & LIMBACH L.L.P.
 Attn. WARD, M.
 2001 Ferry Building
 SAN FRANCISCO, CALIFORNIA 94111-4262
 UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

09/03/2000

Applicant's or agent's file reference

XGEN-110 PCT

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.

PCT/US 99/ 23277

International filing date
(day/month/year)

06/10/1999

Applicant

XGENE CORPORATION et al.

Due 5/9/00

1. The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Nina Vercio
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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference XGEN-110 PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/ 23277	International filing date (day/month/year) 06/10/1999	(Earliest) Priority Date (day/month/year) 09/10/1998
Applicant XGENE CORPORATION et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of invention is lacking (see Box II).

4. With regard to the **title**,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 99/23277

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT
--

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 760 025 A (INST NAT SANTE RECH MED) 28 August 1998 (1998-08-28) the whole document ---	1-55
A	WO 96 28571 A (RECH INVESTISSEMENT SOC FR DE ; PROVOT CHRISTIAN (FR); SALLES BERNAR) 19 September 1996 (1996-09-19) the whole document ---	1-55
A	EP 0 628 817 A (TNO) 14 December 1994 (1994-12-14) the whole document ---	1-55 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

24 February 2000

09/03/2000

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hagenmaier, S

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 99/23277

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MICHELOTTI ET AL.: "MULTIPLE SINGLE-STRANDED CIS-ELEMENTS ARE ASSOCIATED WITH ACTIVATED CHROMATIN OF THE HUMAN C-MYC GENE IN VIVO" MOL.CELL.BIOL., vol. 16, no. 6, 1996, pages 2656-2669, XP002131441 the whole document ----	1-55
A	EVANS ET AL.: "S1-HYPERSENSITIVE SITES IN EUKARYOTIC PROMOTER REGIONS" NUCLEIC ACIDS RESEARCH, vol. 12, no. 21, 1984, pages 8043-8058, XP002131122 the whole document ----	1-55
A	STEWART ET AL.: "RAPID INDUCTION OF c-fos TRANSCRIPTION REVEALS QUANTITATIVE LINKAGE OF RNA POLYMERASE II AND DNA TOPOISOMERASE I ENZYME ACTIVITIES" CELL, vol. 60, 1990, pages 141-149, XP002131034 the whole document ----	1-55
A	WANG AND ROEDER: "DNA TOPOISOMERASE I AND PC4 CAN INTERACT WITH HUMAN TFIIIC TO PROMOTE BOTH ACCURATE TERMINATION AND TRANSCRIPTION REINITIATION BY RNA POLYMERASE III" MOL.CELL, vol. 1, April 1998 (1998-04), pages 749-757, XP002131035 the whole document ----	1-55
A	FRIEDBERG E C: "RELATIONSHIPS BETWEEN DNA REPAIR AND TRANSCRIPTION" ANNUAL REVIEW OF BIOCHEMISTRY, US, PALTO ALTO, CA, vol. 65, 1 January 1996 (1996-01-01), pages 15-42, XP002047711 the whole document ----	1-55
A	EP 0 441 483 A (BAYLOR COLLEGE MEDICINE) 14 August 1991 (1991-08-14) the whole document ----	1-55

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/23277

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
FR 2760025	A	28-08-1998	WO	9837233 A		27-08-1998
WO 9628571	A	19-09-1996	FR	2731711 A		20-09-1996
			AU	5008996 A		02-10-1996
			CA	2215493 A		19-09-1996
			EP	0815260 A		07-01-1998
			JP	11510362 T		14-09-1999
EP 0628817	A	14-12-1994		NONE		
EP 0441483	A	14-08-1991	AU	4493393 A		18-11-1993
			AU	637446 B		27-05-1993
			AU	6935291 A		18-07-1991
			CA	2034220 A		17-07-1991
			EP	0752477 A		08-01-1997
			JP	6022766 A		01-02-1994

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

09/622703

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) XGEN-110 PCT

Box No. I TITLE OF INVENTION

METHOD FOR DETERMINING TRANSCRIPTION FACTOR ACTIVITY AND ITS TECHNICAL USES

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

XGENE CORPORATION
863C Mitten Road
Burlington, California 94010
United States of America

This person is also inventor.

Telephone No.
(650) 259-0690

Facsimile No.

Teleprinter No.

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box for the purposes of:

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

HOEFFLER, Warren
2028 Howard Avenue
San Carlos, California 94070
United States of America

This person is:

applicant only

applicant and inventor

inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box for the purposes of:

Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

agent common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

WARD, Michael R.
LIMBACH & LIMBACH L.L.P.
2001 Ferry Building
San Francisco, California 94111-4262
United States of America

Telephone No.
(415) 433-4150

Facsimile No.
(415) 433-8716

Teleprinter No.

Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

AP ARIPO Patent: **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

EA Eurasian Patent: **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

EP European Patent: **AT** Austria, **BE** Belgium, **CH** and **LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

OA OAPI Patent: **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

<input checked="" type="checkbox"/> AL Albania	<input checked="" type="checkbox"/> LS Lesotho
<input checked="" type="checkbox"/> AM Armenia	<input checked="" type="checkbox"/> LT Lithuania
<input checked="" type="checkbox"/> AT Austria	<input checked="" type="checkbox"/> LU Luxembourg
<input checked="" type="checkbox"/> AU Australia	<input checked="" type="checkbox"/> LV Latvia
<input checked="" type="checkbox"/> AZ Azerbaijan	<input checked="" type="checkbox"/> MD Republic of Moldova
<input checked="" type="checkbox"/> BA Bosnia and Herzegovina	<input checked="" type="checkbox"/> MG Madagascar
<input checked="" type="checkbox"/> BB Barbados	<input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia
<input checked="" type="checkbox"/> BG Bulgaria	<input checked="" type="checkbox"/> MN Mongolia
<input checked="" type="checkbox"/> BR Brazil	<input checked="" type="checkbox"/> MW Malawi
<input checked="" type="checkbox"/> BY Belarus	<input checked="" type="checkbox"/> MX Mexico
<input checked="" type="checkbox"/> CA Canada	<input checked="" type="checkbox"/> NO Norway
<input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein	<input checked="" type="checkbox"/> NZ New Zealand
<input checked="" type="checkbox"/> CN China	<input checked="" type="checkbox"/> PL Poland
<input checked="" type="checkbox"/> CU Cuba	<input checked="" type="checkbox"/> PT Portugal
<input checked="" type="checkbox"/> CZ Czech Republic	<input checked="" type="checkbox"/> RO Romania
<input checked="" type="checkbox"/> DE Germany	<input checked="" type="checkbox"/> RU Russian Federation
<input checked="" type="checkbox"/> DK Denmark	<input checked="" type="checkbox"/> SD Sudan
<input checked="" type="checkbox"/> EE Estonia	<input checked="" type="checkbox"/> SE Sweden
<input checked="" type="checkbox"/> ES Spain	<input checked="" type="checkbox"/> SG Singapore
<input checked="" type="checkbox"/> FI Finland	<input checked="" type="checkbox"/> SI Slovenia
<input checked="" type="checkbox"/> GB United Kingdom	<input checked="" type="checkbox"/> SK Slovakia
<input checked="" type="checkbox"/> GD Grenada	<input checked="" type="checkbox"/> SL Sierra Leone
<input checked="" type="checkbox"/> GE Georgia	<input checked="" type="checkbox"/> TJ Tajikistan
<input checked="" type="checkbox"/> GH Ghana	<input checked="" type="checkbox"/> TM Turkmenistan
<input checked="" type="checkbox"/> GM Gambia	<input checked="" type="checkbox"/> TR Turkey
<input checked="" type="checkbox"/> HR Croatia	<input checked="" type="checkbox"/> TT Trinidad and Tobago
<input checked="" type="checkbox"/> HU Hungary	<input checked="" type="checkbox"/> UA Ukraine
<input checked="" type="checkbox"/> ID Indonesia	<input checked="" type="checkbox"/> UG Uganda
<input checked="" type="checkbox"/> IL Israel	<input checked="" type="checkbox"/> US United States of America
<input checked="" type="checkbox"/> IN India	<input checked="" type="checkbox"/> UZ Uzbekistan
<input checked="" type="checkbox"/> IS Iceland	<input checked="" type="checkbox"/> VN Viet Nam
<input checked="" type="checkbox"/> JP Japan	<input checked="" type="checkbox"/> YU Yugoslavia
<input checked="" type="checkbox"/> KE Kenya	<input checked="" type="checkbox"/> ZW Zimbabwe
<input checked="" type="checkbox"/> KG Kyrgyzstan	
<input checked="" type="checkbox"/> KP Democratic People's Republic of Korea	
<input checked="" type="checkbox"/> KR Republic of Korea	
<input checked="" type="checkbox"/> KZ Kazakhstan	
<input checked="" type="checkbox"/> LC Saint Lucia	
<input checked="" type="checkbox"/> LK Sri Lanka	
<input checked="" type="checkbox"/> LR Liberia	
<input checked="" type="checkbox"/> AE United Arab Emirates	<input checked="" type="checkbox"/> TZ United Republic
<input checked="" type="checkbox"/> CR Costa Rica	of Tanzania
<input checked="" type="checkbox"/> DM Dominica	<input checked="" type="checkbox"/> ZA South Africa

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

AE United Arab Emirates

CR Costa Rica

DM Dominica

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

Supplemental Box*If the Supplemental Box is not used, this sheet need not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

- (i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
- (ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
- (iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
- (iv) if, in addition to the agent(s) indicated in Box IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
- (v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V., the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
- (vi) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;
- (vii) if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Continuation of Box No. IV

LIMBACH, Karl A.

WARD, Michael R.

LIMBACH, George C.

SAMPSON, Roger S.

UILKEMA, John K.

CHEN, Tina

SMITH, Neil A.

HAMILTON, Charles L.

DEVITT, Veronica C.

SMITH, Andrew V.

YIN, Ronald L.

HOGLUND, Heath W.

SEKIMURA, Gerald T.

McCARTHY, J. Thomas

STALLMAN, Michael A.

ACKERMAN, Joel G.

GIRARD, Philip A.

All attorneys are members or associates of the firm LIMBACH & LIMBACH L.L.P.

POLLOCK, Michael J.

Address, telephone number, and facsimile number of all are indicated in Box IV.

EVERETT, Steven M.

EQUITZ, Alfred A

DALLA VALLE, Mark A.

SAMMUT, Charles P..

PICKERING, Mark C.

COLEMAN JAMES, Patricia

FROST, Kathleen A.

HODES, Alan S.

LIMBACH, Alan A.

LIMBACH, Douglas C.

OH, Seong Kun

KING, Cameron A.

HARRIEL, Kyla L.

MAEDA, Mayumi

TOBIN, Kent J.

Box No. VI PRIORITY CLAIM		Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: * regional Office	international application: receiving Office
item (1) 09 October 1998 (09.10.98)	60/103,803	US		
item (2)				
item (3)				

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1)
 * Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA/ EP	Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year) Number Country (or regional Office)		
---	---	--	--

Box No. VIII CHECK LIST: LANGUAGE OF FILING

This international application contains the following number of sheets:	This international application is accompanied by the item(s) marked below:
request : 4	1. <input checked="" type="checkbox"/> fee calculation sheet unsigned
description (excluding sequence listing part) : 47	2. <input checked="" type="checkbox"/> separate signed power of attorney
claims : 7	3. <input type="checkbox"/> copy of general power of attorney; reference number, if any:
abstract : 1	4. <input type="checkbox"/> statement explaining lack of signature
drawings : 5	5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s):
sequence listing part of description	6. <input type="checkbox"/> translation of international application into (language):
Total number of sheets : 64	7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material
	8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form
	9. <input checked="" type="checkbox"/> other (specify): Transmittal Letter, Express Mail Certificate, Return Postcard

Figure of the drawings which should accompany the abstract:

Language of filing of the international application:

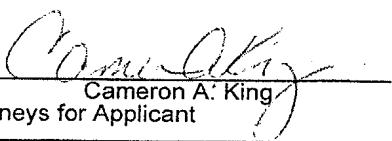
English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

LIMBACH & LIMBACH L.L.P.

By


Cameron A. King

Attorneys for Applicant

1. Date of actual receipt of the purported international application:		For receiving Office use only		2. Drawings:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:				<input type="checkbox"/> received: <input type="checkbox"/> not received:
4. Date of timely receipt of the required corrections under PCT Article 11(2):				
5. International Searching Authority (if two or more are competent): ISA/		6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid		

Date of receipt of the record copy by the International Bureau:

For International Bureau use only

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FR 96/00391A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12Q1/68 C12Q1/18 C12Q1/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NUCLEIC ACIDS RESEARCH, vol. 22, no. 23, November 1994, pages 4937-42, XP002008619 CALSOU P ET AL: "properties of damage-dependent DNA incision by nucleotide excision repair in human cell-free extracts" see the whole document --- BIOCHEM BIOPHYS RES COMMUN, vol. 202, no. 2, July 1994, pages 788-795, XP002008620 CALSOU P ET AL: "measurement of damage-specific DNA incision by nucleotide excision repair in vitro" cited in the application see the whole document --- -/-	1-4,12
X		1-4,12

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

- 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- 'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- 'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- '&' document member of the same patent family

Date of the actual completion of the international search 17 July 1996	Date of mailing of the international search report 25.07.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+ 31-70) 340-3016	Authorized officer Osborne, H

INTERNATIONAL SEARCH REPORT

International Application No
PC1/FR 96/00391

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 472 482 (SRFI) 26 February 1992 cited in the application see the whole document ---	1-4, 16-18
A	EP,A,0 229 674 (PERO R) 22 July 1987 see the whole document ---	16-18
A	WO,A,92 17610 (NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATURWETENSCHAPPELIJK ONDERZ.) 15 October 1992 see the whole document ---	16-18
A	EP,A,0 261 955 (DU PONT DE NAMOURS CO.) 30 March 1988 see the whole document -----	17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/FR 96/00391

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-472482	26-02-92	FR-A-	2666096	28-02-92
		CA-A-	2049166	22-02-92
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		EP-A-	0581801	09-02-94
EP-A-261955	30-03-88	JP-A-	63098400	28-04-88

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FIGURE 1

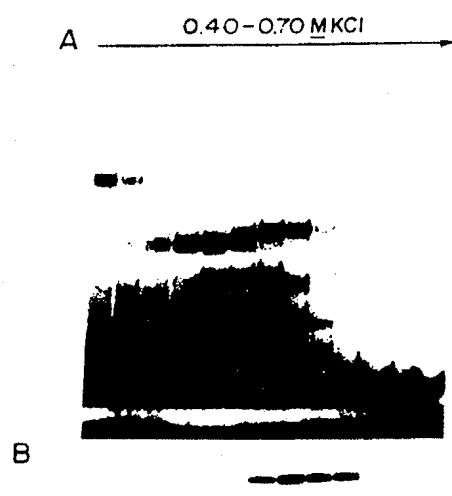


FIGURE 2

3 / 5

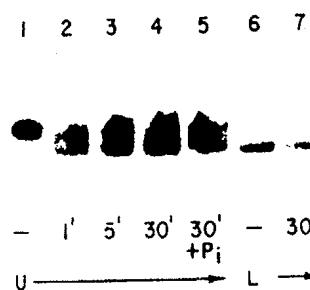
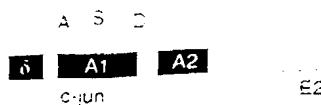


FIGURE 3

4 / 5



3

73AE2
wtE2

4 4

1 2 3 4

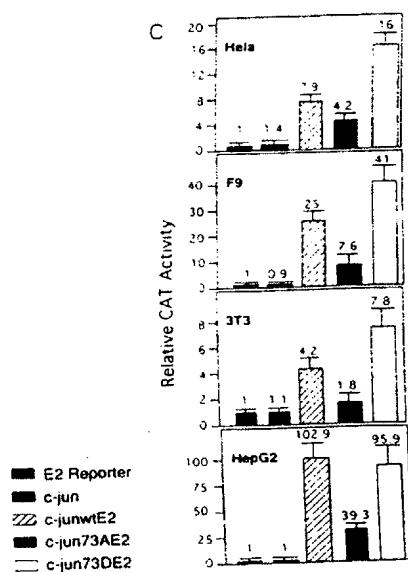


FIGURE 4

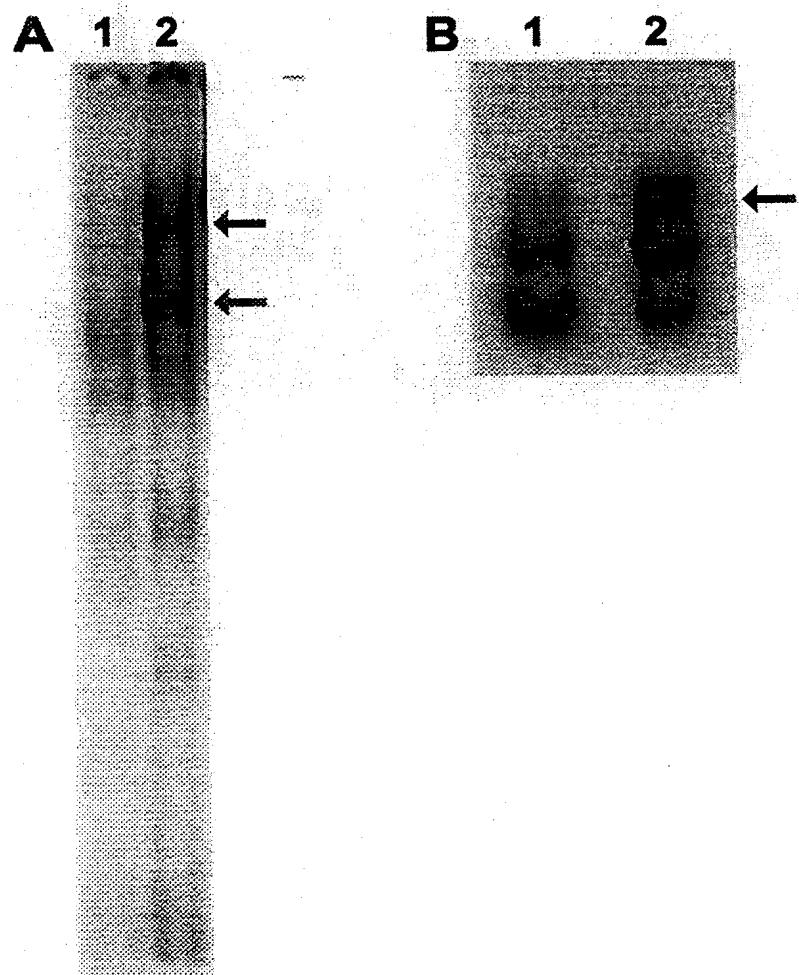


FIGURE 5A

FIGURE 5B

INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

WARD, Michael R. et al
 LIMBACH & LIMBACH L.L.P.
 2001 Ferry Building
 SAN FRANCISCO, CALIFORNIA 94111-4262
 ETATS-UNIS D'AMERIQUE

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JUN 24 2000

WRITTEN OPINION

Limbach & Limbach

(PCT Rule 66)

Date of mailing
 (day/month/year)

13.07.2000

REPLY DUE

within 3 month(s)
 from the above date of mailing

Applicant's or agent's file reference

XGEN-110 PCT

International application No.
 PCT/US99/23277 ✓

International filing date (day/month/year)
 06/10/1999 ✓

Priority date (day/month/year)
 09/10/1998 ✓

International Patent Classification (IPC) or both national classification and IPC

C12Q1/68

Applicant

XGENE CORPORATION et al.

*Resp Due: 10/13/00
 cal. 8 months*

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I Basis of the opinion
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain document cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 09/02/2001.

Name and mailing address of the international preliminary examining authority:



European Patent Office
 D-80298 Munich
 Tel. +49 89 2399 - 0 Tx: 523656 epmu d
 Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Tilkorn, A-C

Formalities officer (incl. extension of time limits)
 Digiusto, M
 Telephone No. +49 89 2399 8162



I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-47 as originally filed

Claims, No.:

1-55 as originally filed

Drawings, sheets:

1/5-5/5 as originally filed

2. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- the entire international application,
- claims Nos. 1-9,15-20,46-54,

because:

- the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for the said claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

Novelty (N)	Claims 21-23,25,29,32-37,55
Inventive step (IS)	Claims 24,26-28,30,31,38-45
Industrial applicability (IA)	Claims

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Claim 1 does not appear to satisfy Art 5 PCT, because the presence of a nick in a DNA molecule is not in all cases caused by a transcription factor. Mutagenic agents, oxidative stress, radiation (see e.g. D3 p 21 37-41) or DNA-topoisomerase II activity for example introduce nicks in a DNA molecule. Hence, it is not possible to conclude that there is transcription activity if a nick is detected in a DNA molecule. Consequently, the method as defined in claim 1 is insufficient to enable the skilled person to carry out the invention (Guidelines II 4.10). The same argument applies to the dependent **claims 2-9**.

Similarly, the methods of independent **claims 15** and **46** conclude from the detection of nicks in a DNA template that an active transcription factor is present in the reaction mixture. As nicks can be caused by various agents (see above), these claims and the corresponding dependent **claims 16-20, 47-54** do not comply with Art 5 PCT, either. As **claim 55** relies on the method of claim 46, it does not comply with Art 5 PCT either. Consequently, no meaningful opinion can be formed on novelty, inventive step and industrial applicability of the above claims (Art 34 (4)(a)(ii) PCT).

Re Item V

The following documents are referred to in this communication:

- D1: WO 90/05745
- D2: Cell (1988) **53** 907-920
- D3: EP-A-0 628 817
- D4: Nucl. Acids Res. (1994) **22(7)** 1305-1312
- D5: Fr-A-2 760 025

D1, D2 and D4 are cited by the examiner (Guidelines VI 7.24). A copy of each of D1, D2 and D4 is appended to this written opinion.

1 Novelty (Art 33(2)PCT):

- 1.1 **Claim 21** is not novel in view of D1 (D1: claims 10 and 11).
A DNA sequence to be transcribed comprising a consensus binding site for a

nicking transcription factor according to claim 21 corresponds to the DNA of the eukaryotic host cell of D1 (D1: claim 10 and 11).

Contacting the DNA sequence with a nicking transcription factor according to claim 21 corresponds to transforming the eukaryotic host cell with a construct comprising a eukaryotic promoter operably linked to the CREB protein and culturing said transformed host cells. The construct provides for the expression of the CREB protein in the cell. As shown in the present application, CREB is a nicking transcription factor. Since the method of D1 is aimed at increasing the transcription level, the CREB protein, the transcription factor which is expressed in the cell, must bind to its target, namely the DNA sequence comprising a consensus binding site to initiate transcription. Similarly, **claims 22, 23 and 25** (D1: mammalian cell: p 13 para 3; yeast: p 14 para 3; insect cell: p 15 para 2) are not novel.

The technical features of the method of **claim 29** correspond to the method features of D1 as set forth above. Thus, since CREB binds to its target on the DNA and stimulates transcription, it must produce a single-stranded nick in the DNA molecule, because according to the invention CREB is a nicking transcription factor (appl.: p 16 l 30 - p 18 l 13; Fig 5). Hence, **claim 29** is not novel, either.

1.2 **Claims 32-37** are not novel, because the only technical features of the kit are formulated in terms of process features of known processes:

- sequencing reaction (see citations in the application: p 25 para 3 ff; p 30 para 1 ff; p 32 para 2 ff);
- electrophoretic gel (D5: p 14 Example 4)
- SI nuclease assay (appl.:p 24 para 4)

1.3 **Claim 55** is not novel because CREB is a transcription factors that falls within the scope of the claim since it is a nicking transcription factor and should therefore be identifiable by the method of claim 46. For the assessment of claims directed to products defined by their process of manufacture, on the question of whether they are novel, no unified criteria exist in the PCT. The EPO, for example, does not recognize as novel the subject-matter of claims to known products defined in terms of a process of manufacture, since it is considered that a product is not rendered novel merely by the fact that it is produced by means of a new process.

- 1.4 **Claim 10** is novel, because none of the available documents discloses a method for detecting transcription activity that involves the detection of a nick in the DNA template. Accordingly, dependent **claims 11-14** are also novel.
- 1.5 **Claim 24** is novel, because none of the available documents discloses a method of modulating transcription activity carried out on a human cell. Similarly, no method on monocot or dicot cells has previously been disclosed (**claim 26**).
- 1.6 **Claim 27** is novel, because none of the available documents discloses a method of modulating transcription activity using a nicking transcription factor that has been phosphorylated *in vitro*. Furthermore, **claim 28** relating to a method that involves a recombinant nicking transcription factor containing an amino acid substitution is novel over the available prior art. The same arguments apply to **claims 30** and **31**, respectively.
- 1.7 **Claim 38** is novel, because none of the available documents discloses a kit comprising a DNA template with a consensus sequence for a nicking transcription factor and a detection agent for the identification of a nicked DNA template. Accordingly, dependent **claims 39-45** are also novel.

2 Inventive Step (Art 33(3)PCT):

- 2.1 **Claim 24** and **26** appear to relate to straightforward modifications of the known method of claim 21 (see V 1.1 above) and thus do not appear to involve an inventive concept.
- 2.2 **Claims 27** and **28** do not seem to satisfy Art 33(3)PCT for the following reasons: The additional features over claim 21 are the *in vitro* phosphorylation and the amino acid substitution respectively. The problem to be solved can thus be regarded as the provision of a means for activating transcription factors. Phosphorylated transcription factors are known to be the active form of transcription factors (see D2: Fig. 7 and 9). Moreover, it has previously been disclosed for some transcription factors that substitution of aspartic acid results in higher transcription activity of the respective transcription factor (see D4: Fig. 6).

Actually, the Figures 1-4 of the present application are taken from D2 (Fig 5,7,9) and D4 (Fig. 6) and they form the basis for the embodiments of claims 27 and 28. Thus, the combination of the method of D1 with the teaching of D2 and D4 renders the embodiments of **claims 27 and 28** obvious for the skilled person. The same arguments apply to **claims 30 and 31**, which do not seem to be inventive in view of D1 and D2 or D4, either.

2.3 **Claim 38** does not appear to be inventive for the following reasons:

The technical features of the claim are formulated as functional features. A DNA template comprising a consensus sequence for a nicking transcription factor is e.g. comprised in a sample of complete genomic DNA of an organism. A reagent for the detection of a nicked DNA template encompasses reagents for electrophoretic gels e.g. polyacrylamid gels.

D5 describes a method for screening of cytotoxic mutagenic products (p 6 | 22-31). The basic method consists of the detection of damaged DNA using TBP (TATA binding protein). It is shown in D5 that TBP specifically binds to nicked DNA (p 2 | 8-12). Apparently, nicking DNA leads to a change in the 3D structure of the DNA which enables the TBP to bind and to form a TBP/nicked DNA complex. On an electrophoretic gel, a complex of nicked DNA/ TBP shows lower mobility than undamaged DNA alone, which can be detected by a labelled DNA probe (Example 4, p 14). The DNA used in the experiments of D5 is total genomic DNA of HeLa cells (p 8 | 13).

In conclusion, the method of D5 includes all the technical features of claim 38. In order to economically exploit this method the skilled person would put together a kit that comprises genomic DNA, TBP and a labelled DNA probe. The preparation of a kit using known components is not considered to be inventive. Thus, claim 38 does not appear to involve inventive activity (Art 33(3)PCT). The same applies to claims 41 and 42 because the method of D5 involve ^{32}P labelled DNA probes (p 14 | 20-25)

Moreover, D5 discloses an embodiment, in which the TBP is immobilized on a nitrocellulose membrane and potentially nicked DNA is allowed to bind. The amount of bound DNA enables the quantification of nicked DNA (p 5 | 11-15).

Claims 39 and 40 relate to embodiments involving the immobilization of the DNA template. The labelling of a detection agent or the DNA template is an arbitrary choice which is well known in the art. Hence, **claims 39 and 40** do not seem to be

inventive either.

2.4 If the Applicant overcomes the objection raised under Section VIII 1. below, **claim 10** appears to satisfy Art 33(3)PCT for the following reasons:

Claim 10 differs from the disclosure of D1, which is considered to represent the closest prior art, in that D1 does not disclose a step of detecting the presence or absence of a nick in the DNA template.

The problem to be solved can thus be regarded as the provision of a method for the detection of transcription activity.

Since the nicking effect of transcription factors is first described in the present application, the detection of a nick in a template DNA that has been treated with a transcription factor seems to be an inventive method for the detection of transcription activity. Consequently, also **claims 11-14** appear to satisfy Art 33(3) PCT.

Re Item VII

- The expression "incorporated herein by reference" in respect of prior art documents (e.g. page 21 para 2; p 25 para 3; p 38 para 1; p 47 para 1) leads to a doubt as to whether the requirement of the description being self-contained is satisfied (Guidelines II, 4.17).
- The last paragraph on page 47 should be deleted as it contains general statements which imply that the extent of protection may be expanded in some vague and not precisely defined way (Guidelines III 4.3a).

Re Item VIII

1. **Claims 1-31, 46-55** are not sufficiently supported by the description (Art 6 PCT; Guidelines III 6.3). Experimental evidence for the link between transcriptional activity and nicking activity is presented only for one transcription factor, namely for CREB (p 16 l 30 - p 18 l 13; Fig. 5B). For the other transcription factors mentioned in the application (TIIIC; C-Jun, BPV-E2; c-Jun/BPV-E2) only the two band structure on an electrophoretic gel is shown (Fig. 2; Fig. 4, p 15 l 22-31). This structure can result from different forms of the transcription factor protein as

assumed in the state of the art (appl.: p 12 l 24- 29) and there is no experimental basis found throughout the application for the assumption that TIIIC, c-Jun, BPV-E2 or c-Jun/BPV-E2 cause DNA nicks. Hence, in order to overcome this objection, the claims should be restricted to methods relying on CREB transcription factor.

2. **Claim 24** does not satisfy Art 6 PCT, because the expression "said mammalian cell" is not clear, as there is no previous mention of any mammalian cell.

PATENT COOPERATION TREATY

EXPRESS MAIL LABEL NO. EL254116444US
Attorney Docket No. XGEN-110 USA

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LIMBACH & LIMBACH L.L.P.

From the INTERNATIONAL SEARCHING AUTHORITY

To:
LIMBACH & LIMBACH L.L.P.
Attn. WARD, M.
2001 Ferry Building
SAN FRANCISCO, CALIFORNIA 94111-4262
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

09/03/2000

Applicant's or agent's file reference XGEN-110 PCT	FOR FURTHER ACTION	See paragraphs 1 and 4 below
International application No. PCT/US 99/ 23277	International filing date (day/month/year)	06/10/1999
Applicant XGENE CORPORATION et al.	<i>Due 5/9/00</i>	

1. The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Nina Vercio
---	---------------------------------------

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference XGEN-110 PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/ 23277	International filing date (day/month/year) 06/10/1999	(Earliest) Priority Date (day/month/year) 09/10/1998
Applicant XGENE CORPORATION et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. **Certain claims were found unsearchable** (See Box I).

3. **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/23277

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 760 025 A (INST NAT SANTE RECH MED) 28 August 1998 (1998-08-28) the whole document ---	1-55
A	WO 96 28571 A (RECH INVESTISSEMENT SOC FR DE ;PROVOT CHRISTIAN (FR); SALLES BERNAR) 19 September 1996 (1996-09-19) the whole document ---	1-55
A	EP 0 628 817 A (TNO) 14 December 1994 (1994-12-14) the whole document ---	1-55

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

24 February 2000

09/03/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Hagenmaier, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/23277

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MICHELOTTI ET AL.: "MULTIPLE SINGLE-STRANDED CIS-ELEMENTS ARE ASSOCIATED WITH ACTIVATED CHROMATIN OF THE HUMAN C-MYC GENE IN VIVO" MOL.CELL.BIOL., vol. 16, no. 6, 1996, pages 2656-2669, XP002131441 the whole document ---	1-55
A	EVANS ET AL.: "S1-HYPERSENSITIVE SITES IN EUKARYOTIC PROMOTER REGIONS" NUCLEIC ACIDS RESEARCH, vol. 12, no. 21, 1984, pages 8043-8058, XP002131122 the whole document ---	1-55
A	STEWART ET AL.: "RAPID INDUCTION OF c-fos TRANSCRIPTION REVEALS QUANTITATIVE LINKAGE OF RNA POLYMERASE II AND DNA TOPOISOMERASE I ENZYME ACTIVITIES" CELL, vol. 60, 1990, pages 141-149, XP002131034 the whole document ---	1-55
A	WANG AND ROEDER: "DNA TOPOISOMERASE I AND PC4 CAN INTERACT WITH HUMAN TFIIIC TO PROMOTE BOTH ACCURATE TERMINATION AND TRANSCRIPTION REINITIATION BY RNA POLYMERASE III" MOL.CELL, vol. 1, April 1998 (1998-04), pages 749-757, XP002131035 the whole document ---	1-55
A	FRIEDBERG E C: "RELATIONSHIPS BETWEEN DNA REPAIR AND TRANSCRIPTION" ANNUAL REVIEW OF BIOCHEMISTRY, US, PALTO ALTO, CA, vol. 65, 1 January 1996 (1996-01-01), pages 15-42, XP002047711 the whole document ---	1-55
A	EP 0 441 483 A (BAYLOR COLLEGE MEDICINE) 14 August 1991 (1991-08-14) the whole document -----	1-55

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/23277

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR 2760025	A 28-08-1998	WO	9837233 A	27-08-1998
WO 9628571	A 19-09-1996	FR	2731711 A	20-09-1996
		AU	5008996 A	02-10-1996
		CA	2215493 A	19-09-1996
		EP	0815260 A	07-01-1998
		JP	11510362 T	14-09-1999
EP 0628817	A 14-12-1994	NONE		
EP 0441483	A 14-08-1991	AU	4493393 A	18-11-1993
		AU	637446 B	27-05-1993
		AU	6935291 A	18-07-1991
		CA	2034220 A	17-07-1991
		EP	0752477 A	08-01-1997
		JP	6022766 A	01-02-1994

PATENT COOPERATION TREATY

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MAY 15 2000

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LIMBACH & LIMBACH L.L.P.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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LIMBACH & LIMBACH L.L.P.
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NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))Date of mailing
(day/month/year)

09.05.00

Applicant's or agent's file reference
XGEN-110 PCT

IMPORTANT NOTIFICATION

International application No.
PCT/US 99/ 23277

International filing date (day/month/year)

06/10/1999

Priority date (day/month/year)

09/10/1998

Applicant

XGENE CORPORATION et al.

1. The applicant is hereby **notified** that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

20/04/2000

2. This date of receipt is:

the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
 the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
 the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

(*If applicable*) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/

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